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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,997	KRISHNAN ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/8/05, 2/14/05, 12/23/04, 12/16/04 and 6 1/14/04 and 2/19/04

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-48 is/are pending in the application.

4a) Of the above claim(s) 15,17 and 20-48 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14,16,18 and 19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/14/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-48 are pending in the application as of the response received on July 8, 2005, with claims 15, 17 and 20-48 being withdrawn from further consideration as being drawn to a non-elected invention.

Election/Restrictions

Applicant's election with traverse of the claims of Group I, namely claims 1-14, 16 and 18-19 in the reply filed on July 8, 2005 is acknowledged. The traversal is on the ground(s) that searching for the product as well as the method of making and using the product would not pose an undue search burden on the Office. This is not found persuasive because, while the searches of Groups I, II and III may to some extent overlap due to their similar classification, there is no reason to believe that the searches would be co-extensive. In searching Group I, the Examiner will be focusing on the patentability of the product itself, and not the processes of Groups II and III. Conversely, in searching Groups II and III, the Examiner would be required to focus on the patentability of the processes and not the composition. Accordingly, a search for both groups would pose an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL. The claims drawn to Groups II and III are withdrawn from consideration as being drawn to non-elected inventions.

Applicant's election without traverse of the species is acknowledged. Applicant has elected the species itraconazole as the antifungal active pharmaceutical component, microcrystalline cellulose as the bulking agent, croscarmellose sodium as the disintegrant, polyvinyl pyrrolidone as the binding agent, and hydrochloric acid as the acid. The claimed subject matter that is not drawn to the elected species is withdrawn from further consideration as being drawn to non-elected subject matter.

Accordingly, the claims of Groups II and III, namely claims 15, 17 and 20-48 are withdrawn from further consideration as being drawn to non-elected inventions.

Priority

Applicant's claim of foreign priority to INDIA 1231/MUM/2003 11/28/2003 is acknowledged.

Claim Objections

Claim 16 is objected to due to a typo-type error because mannitol and microcrystalline cellulose are erroneously recited as being "binding agents," when in fact these materials are described as "bulking agents" in the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for lacking antecedent basis for the term "third disintegrant." Claims 1 and 11, from which claim 14 depends, do not recite a "third disintegrant," and thus claim 14 is unclear because it is not clear what "third disintegrant" is being referred to. Accordingly, as the metes and bounds of claim 14 cannot be determined, the claim is indefinite. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14, 16 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,346,533 to Cha et al, issued February 12, 2002, in

view of U.S. Patent No. 5,707,975 to Francois et al, issued January 13, 1998, U.S. Patent No. 6,509,038 to Baert et al, issued January 21, 2003, and U.S. Patent Application Publication No. 2003/0104066 to Murai et al, published June 5, 2003.

Cha et al. teaches a pharmaceutical composition for oral administration of itraconazole that exhibits improved solubility and bioavailability (see column 1, lines 10-67, in particular.) Cha et al. teaches that solubility of the drug is improved by dissolving the itraconazole in an organic solvent and dissolution drying the mixture to form particles (see column 2, lines 1-10, in particular.) Cha et al. exemplifies a method of dissolution drying spray drying as well as via a fluid bed granulator (see Examples 2-3, column 3, line 54 through column 4, lines 10, in particular), which is the same granulation method exemplified in Examples 1-3 of Applicant's specification. Cha et al. teaches that pharmaceutical excipients can also be provided in the dissolution-induced drying step, including a binder, a disintegrant, a stabilizer, or another active material (see column 2, line 63 through column 3, lines 2, in particular.) Cha et al. furthermore exemplifies compositions that are uniformly mixed (see column 4, lines 25-35, in particular), and thus is considered to teach granules having itraconazole distributed uniformly throughout.

Regarding claim 2, Cha et al. teaches that the composition can be provided in the form of a tablet or capsule (see column 3, lines 34-48, in particular.) Regarding claim 3, Cha et al. teaches providing itraconazole.

Cha et al. does not specifically teach granules that are non-spherical. Cha et al. also does not specifically teach part (b) of claims 1 and 16, namely providing a bulking agent that is microcrystalline cellulose. Cha et al. furthermore does not specifically teach granules having a disintegrant that is croscarmellose sodium (part (c)), a binding agent that is polyvinyl pyrrolidone (part (d)) or an acid that is hydrochloric acid (part (e)), as recited in claims 1 and 16.

Regarding part (e) of claim 1 and also claim 8, namely the limitation that the acid is hydrochloric acid, the teachings of Francois et al. are noted. Francois et al. teaches a formulation for oral administration of an antifungal agent (see abstract, in particular.) Francois et al. teaches that antifungal agents such as itraconazole have improved solubility and dissolution rate in organic solvents comprising alcoholic co-solvents, such as ethanol, combined with an acidic medium, such as a hydrochloric acid solution (see column 1, lines 5-50 and column 3, lines 40-67, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention as made would have found it obvious to substitute the hydrochloric acid-containing solvent of Francois et al. into the granule preparation method of Cha et al, and thereby forming granules having hydrochloric acid, because Cha et al. teaches the itraconazole is dissolved in an organic solvent prior to dissolution drying, and Francois et al. teaches an organic solvent comprising hydrochloric acid that exhibits a good dissolution of

itraconazole. Thus, one of ordinary skill in the art would have been motivated to provide the hydrochloric-acid containing solvent medium of Francois et al. in the method of Cha et al, thereby forming granules containing hydrochloric acid, with the expectation of providing a solvent medium suitable for dissolving the itraconazole drug prior to the dissolution drying step.

Regarding parts (b) and (c) of claim 1 and also claims 4-5, it is noted that Baert et al. teaches antifungal compositions with improved bioavailability having particles comprising itraconazole (see abstract, in particular.) Baert et al. teaches that suitable disintegrants that can be provided with the itraconazole particles can include crosslinked sodium carboxymethylcellulose (croscarmellose sodium.) (See column 8, lines 31-45, in particular.) Baert et al. further teaches that the composition can comprise a diluent or filler (bulking agent) to provide the desired disintegration rate and bioavailability of the itraconazole, and that suitable diluents or fillers can comprise microcrystalline cellulose.)

Regarding part (d) of claim 1 and also claim 7, it is noted that Murai et al. teaches easy-to-take granules comprising an active ingredient, such as itraconazole (see abstract and paragraph 39, in particular.) Murai et al. teaches that a binder suitable for such a granulated composition can include polyvinyl pyrrolidone (see paragraph 42, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the microcrystalline cellulose bulking agent and croscarmellose sodium disintegrant of Baert et al. and the polyvinylpyrrolidone binder of Murai et al. in the composition formed by Cha et al. and Francois et al, because Cha et al. and Francois et al. teach forming granules which can include a binder a disintegrant or another active material, and Baert et al, and Murai et al. teach disintegrants, active materials comprising fillers or diluents, and binders that are suitable for oral compositions comprising particles. Accordingly, one of ordinary skill in the art would have been motivated to provide the disintegrant, filler and binder of Baert et al. and Murai et al. in the granule composition of Cha et al. and Francois et al. with the expectation of providing suitable pharmaceutical excipients in the granule composition.

Regarding the limitation that the composition comprises non-spherical granules as in claim 1, it is noted that Applicant's guidance in the specification as to the means of formation of the claimed non-spherical granules is limited to a description of the composition used to form the granules, and a statement that the granules are generated from the composition via a fluid bed granulator (as in Examples 1-3 of Applicant's specification, for example.) As discussed above, the teachings of Cha et al, Francois et al, Baert et al. and Murai et al. render the granule composition obvious, and Cha et al. also exemplifies fluid bed granulation as a method of forming the granules (see Example 2, in particular.) Accordingly, it is considered that the claimed non-spherical granules are also rendered obvious by the teachings of Cha et al, Francois et al, Baert

et al, and Murai et al, as the granule-forming method taught by the combined references is the same as that taught in the specification as being capable of generating non-spherical granules.

Accordingly, the combined teachings of Cha et al, Francois et al, Baert et al. and Murai et al. render obvious the pharmaceutical compositions of claims 1-5, 7-9 and 16.

Regarding the disintegrant comprising the mixture of croscarmellose sodium and crospovidone that is recited in claim 6, or the limitation that the granules comprise a second disintegrant as in claims 11-12, it is noted that Baert et al. teaches that suitable disintegrants include croscarmellose sodium as well as crosspovidone (see column 8, lines 31-40, in particular.) Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.) Accordingly, it would have been obvious to provide a combination of the disintegrants taught as being suitable by Baert et al. in the composition of Cha et al, Francois et al, and Murai et al, with the expectation of providing suitable disintegrants for the composition.

Regarding claims the limitation of claims 13-14 that the granules comprise a third disintegrant selected from the group consisting of crospovidone, croscarmellose sodium and sodium starch glycolate, in addition to a second disintegrant, it is noted that Murai et al. also teaches that suitable disintegrators for particle compositions (see paragraph 0036, in particular.) Murai et al. provides examples of multiple disintegrators, including hydroxypropyl starch and corn starch (see paragraph 0036, in particular.) Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to combine one of the disintegrators taught by Murai et al, for example as a second disintegrant, with a first disintegrant comprising croscarmellose sodium and a third disintegrant comprising crospovidone, as taught by Baert et al, and provide the disintegrators in the composition taught by the combination of Cha et al, Francois et al, Baert et al, and Murai et al, with the expectation of providing suitable disintegrants in the composition.

Regarding the limitation recited in claims 9-10 that the granules comprise a cyclodextrin, Francois et al. teaches that the solubility and bioavailability of compounds such as itraconazole is increased by complexation with cyclodextrins (see column 1,

lines 14-26, in particular.) Francois et al. teaches that such solubilizing cyclodextrins include β-cyclodextrin derivatives such as 2-hydroxypropyl-β-cyclodextrin (see column 2, lines 15-20, in particular.) Francois et al. furthermore teaches that cyclodextrins can be provided with the organic solvent comprising the acid and alcoholic co-solvent to improve solubility of itraconazole (see column 3, lines 40-56, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the cyclodextrins of Francois et al. in the composition taught by Cha et al, Baert et al. and Murai et al, with the expectation of improving the solubility and bioavailability of itraconazole in the composition.

Claim 18 differs from the limitations recited in claim 1 in that the claim recites the granules having a croscarmellose sodium and crospovidone mixture, and also recites the granules comprising cyclodextrin. Claim 19 includes the further limitation that the cyclodextrin in hydroxypropyl- β-cyclodextrin. However, as discussed above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide these components as a part of the granule composition of Cha et al, Francois et al, Baert et al, and Murai et al, because Baert et al. teaches that suitable disintegrants for the composition can include croscarmellose sodium and crospovidone, and Francois et al. teaches that cyclodextrins such as hydroxypropyl- β-cyclodextrin improve the solubility and bioavailability of itraconazole. Accordingly, the composition recited in claims 18-19 is rendered obvious by the combined teachings of Cha et al, Francois et al, Baert et al. and Murai et al.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. In particular, U.S. Patent Application Publication No. 2001/0055639 to Moritz et al, published December 27, 2001, teaches that fluidized bed granulation yields irregularly shape granules (see paragraph 0018, in particular.)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 8:30-5:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMC

SREENI PADMANABHAN
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